Cancer Chemother Pharmacol (1986) 16: 178–181

Cancer Chemotherapy and Pharmacology

The effect of dose on the bioavailability of oral etoposide

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Summary. The bioavailability of orally administered etoposide varies considerably. The effect of dose on bioavailability has not previously been investigated. In this study six patients were each treated with oral etoposide at doses of 200, 400, and 600 mg, and the pharmacokinetics determined. Each patient acted as his own control. The area under the plasma concentration-time curve (AUC) was proportionately greatest at the lowest dose. Doubling the dose from 200 mg to 400 mg increased AUC by only 50%, and a further increase of only 2.2% occurred at a dose of 600 mg. These data show nonlinear bioavailability of etoposide within the range in clinical use and may explain the variable results of reported studies. The data may have important implications for chemotherapy regimens with oral etoposide.

Introduction

Etoposide is a semisynthetic podophyllotoxin derivative [14] with major activity in small cell lung carcinoma, germ cell tumours of the testis, the non-Hodgkin's lymphomas, and acute nonlymphocytic leukaemia [1, 15, 21, 25]. It is frequently administered by mouth, usually over several days, at a variety of doses on the basis of a bioavailability of approximately 50% [2, 15, 22, 23]. Whilst bioavailability of this extent has been shown for doses at the lower end [10, 11] and in the middle [4, 7] of the therapeutic range, there is little information on the bioavailability at doses of 400 mg and above [19]. With increasing interest in the effect of both schedule (1 day versus 5 days) and higher doses on the activity of etoposide [6, 26, 27], such information assumes particular importance. Early uncontrolled studies [11] suggested that bioavailability might be decreased at higher doses (400 mg). The relationship between the dose administered and the plasma concentrations achieved has therefore been evaluated prospectively.

Materials and methods

Patients. Six adult patients receiving etoposide for relapsed extensive small cell lung carcinoma (3 patients) or as primary treatment for diffuse malignant mesothelioma (3 patients) were studied. All were ambulant (Karnofsky score $>60\%$ [17]) with normal bone marrow, renal and hepatic function. Gastrointestinal function was clinically normal.

Treatment. Patients received etoposide in capsule form as a single dose after an overnight fast. Therapy was given on 3 successive days at doses of 200 mg, 400 mg, and 600 mg, the order of treatment being randomised. In those patients (with small cell lung carcinoma) receiving the drug as part of a combination regimen, the other drugs (adriamycin and procarbazine) were given on day 4 after the pharmacological studies were complete. The patients with malignant mesothelioma received etoposide alone. Food and drink were permitted ad libitum 4 h after etoposide administration. Antiemetic therapy was not required.

Sampling and assay. After an overnight fast an heparinised polyethylene catheter was introduced into a suitable forearm vein under local anaesthesia. A pretreatment blood sample was taken. After etoposide administration blood samples were then taken at 0.25, 0.5, 0.75, 1. 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h. Blood samples were taken into lithium/heparin tubes, centrifuged, separated, and stored at $-20\,^{\circ}C$ until assay. Urine was collected from the time of etoposide administration for 24 h. The total quantity was measured and an aliquot taken and stored at $-20\,^{\circ}C$ until assay. Assay was performed by reverse-phase high-performance liquid chromatography with a 5-μm ODS Hypersil column (100×5 mm) with methanol-water (51 : 49) solvent at a flow rate of 2 ml/min. Detection was by UV absorbance at 229 nm. The internal standard used was diphenylhydantoin (DPH), and methylphenytoin (MPPH) in patients receiving DPH as an anticonvulsant. This system typically gave retention times of 2.1 min for etoposide, 2.9 min for DPH, and 4.5 min for MPPH. Flow rate and mobile phase methanol content were adjusted as necessary to optimise resolution and retention on different columns. Calibration was achieved by running standard samples and using peak height ratios of etoposide to internal standard [10]. Extraction efficiency was $>80\%$. Lower limit of sensitivity was <100 ng/ml and coefficients of variation were $<4\%$ within run and $<7\%$ between runs.

Calculation and statistics. Pharmacokinetic profiles were plotted by means of Stripe [16], an interactive computer program for the analysis of drug pharmacokinetics. This program calculates AUC by the trapezoidal method ex-

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Table 1. Effect of dose on the pharmacokinetics of etoposide (means ± 95% confidence limits)

	200 mg	400 mg	600 mg
Elimination half-life (h)	9.8± 3.0	7.0± 1.2	7.0± 2.0
Peak plasma concentration (μg/ml)	8.5± 4.4	13.6±13.4	12.5± 8.3
AUC (μg/ml.h/1.7 m^2)	63.9±23.4	95.9±51.8	97.3±28.8
Urinary excretion (% of dose given)	14.0± 6.0	9.0± 4.0	6.0± 3.0

Table 2. Individual patient results: percentage increase in AUC with 400 mg and 600 mg compared with 200 mg dose

Patient	400 mg dose (predicted increase 100%)	600 mg dose (predicted increase 200%)
1	33	59
2	62	39
3	116	66
4	25	103
5	−2	44
6	30	31
Mean	44	57
95% Confidence limits	±43	±27

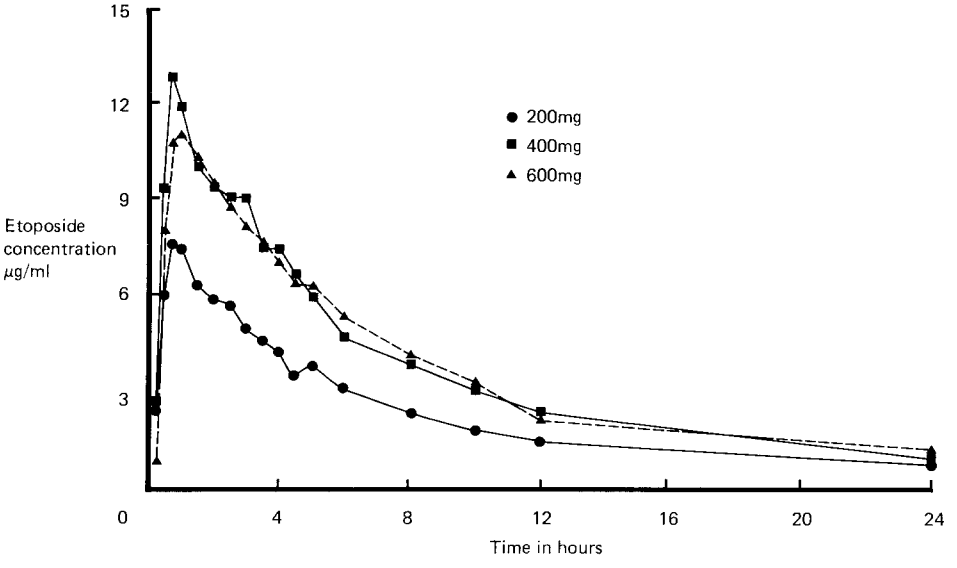

Fig. 1. Mean plasma concentrations of etoposide following oral doses of 200 mg, 400 mg and 600 mg

trapolated to infinity. The effect of residual concentrations from the previous day were removed by curve stripping. The volume of distribution (Vd) was calculated from the formula:

$$Vd = \frac{Dose}{AUC \times k}$$

where k = elimination rate constant, and the clearance (Cl) from the formula:

$$Cl = \frac{Vd \times k}{60}$$

Statistical significance was calculated with reference to Student's *t*-test.

Results

The pharmacokinetic data are given in Table 1 and mean plasma profiles shown in Fig. 1. The elimination half-life of etoposide was unchanged at the different doses. The mean peak plasma concentrations were higher after the 400 mg dose than after the 200-mg dose, but were lower than predicted. There was no further increase with the 600-mg dose. The mean AUC followed the same pattern. The mean AUC increased by only 50% when the dose was doubled from 200 mg to 400 mg, and by only 52% when it was trebled from 200 mg to 600 mg. The relationship between dose and mean AUC is shown in graph form in Fig. 2. The data for individual patients, showing the percentage increase in AUC with increasing dose, are display-

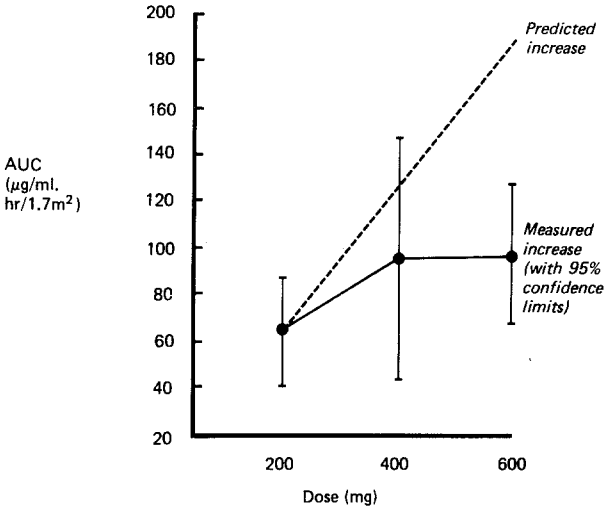

Fig. 2. Comparison of predicted and actual AUC following oral etoposide administration at doses of 200 mg, 400 mg and 600 mg

ed in Table 2. Only one patient achieved the increase predicted at 400 mg, and none at 600 mg.

The urinary excretion of etoposide followed a similar pattern.

Discussion

These data have shown a relative decrease in the AUC achieved at doses of 400 mg and above. Thus, single oral doses of greater than 200 mg resulted in reduced bioavailability, with less than the predicted increase in the dose received by the patient.

The original clinical studies of oral etoposide with the lipophilic capsule suggested low bioavailability at the higher doses and led to the withdrawal of this formulation [4, 5, 20, 25]. Subsequent validation of the currently used hydrophilic capsule was at the lower end of the dose scale – 100 mg in the study by Beveridge et al. [3] and 70–150 mg/m^2 in that by Lau et al [18]. D'Incalci et al. [7], using HPLC to measure etoposide concentrations, found a mean bioavailability of just over 50% (range 29%–137%) for doses of approximately 200 mg/m^2.

The current study has suggested a limit to the effective absorption of etoposide at doses between 200 mg and 400 mg. No previous study has prospectively assessed the bioavailability of increasing doses of oral etoposide. Despite the failure of the 400 mg dose to produce the predicted increase in this study (Fig. 2), the mean AUCs at both 200 mg and 400 mg were in the range expected from previous investigations [10, 11, 24].

It seems unlikely that altered pharmacokinetics can explain these findings. In studies with IV etoposide the AUC achieved increases as predicted with increasing dose [8, 9, 13].

It appears that absorption of etoposide decreases somewhere between 200 and 400 mg. Recovery must be rapid (less than 24 h), however, as indicated by the unchanged pattern of plasma concentration on subsequent days. It is possible that such findings might be explained by a limited area for etoposide absorption in the upper small bowel. Under these circumstances saturation or inhibition of absorption might only be temporary, but by the time of recovery the etoposide would have moved further down the gut and therefore not be absorbed.

The nonlinear absorption of etoposide within the dosage range used clinically may explain variations in the results of reported studies [7, 18, 20]. It makes comparison of the effects of different schedules of oral etoposide (large single doses versus several smaller doses) on outcome impossible. Such comparisons will require IV administration of etoposide for reliable results.

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Received March 28, 1985/Accepted July 24, 1985